Bandolier 149

Independent evidence-based thinking about health care

On conspiracy theories

There are some great websites on conspiracy theories, but be warned, they can suck you in and change your life unless you have a huge prophylactic dose of scepticism and frequent reality checks. But they keep coming, and harm from drugs or medical interventions seems to be favourite for catching headlines these days.

Perhaps the place to start from is that stuff happens. Whatever is done in healthcare, there is an ongoing risk of something bad happening with doing nothing, and the same bad thing when doing something. The problem is establishing causation. The even bigger problem is that really bad things are thankfully rare, so establishing association between a rare bad thing and a particular intervention is going to be awfully difficult.

Rare events are rarely picked up in trials, so the first we know about a potential problem comes from observations by thinking doctors using established reporting systems, or by audits established to seek out bad things. That is good quality control procedures at work, finding out how bad we are.

Early warning, though, does not constitute full understanding of what is going on. An unthinking rush to judgement can do more harm than good; we almost always need more information. An example this month is from TNF antagonists, where randomised trials show one thing, and observational studies another. The difference lies in drugs used, and duration. Another is jaw osteonecrosis with bisphosphonates, with high rates in cancer, but negligible in osteoporosis, with different drugs, doses, and routes of administration involved.

For both examples, enormous benefits accrue in particular clinical circumstances, where few sensible people would cavil at the concomitant risk. Not a good headline, though, is it?

In this issue

Adverse events with TNF antagonists

There is no doubt that TNF-antagonists – antibodies that mop up various forms of TNF in the body – have contributed to substantial benefits for patients with rheumatological and other disorders where the immune system is abnormal. Much greater improvements are now possible, and the benchmarks for treatment have been raised markedly.

That said, fiddling with the immune system brings dangers, including cancer and serious infections. Trying to measure the rate at which these rare events occur, and whether the rates are different with TNF-antagonist treatment is hard because of limited numbers. New studies provide at least some insight, and highlight the problems. It is probably best to look at the evidence from randomised trials first, then compare it with evidence from observational studies.

Randomised trials

A systematic review and meta-analysis [1] used trials of infliximab and adalimumab in rheumatoid arthritis (etanercept was excluded because of a somewhat different mechanism of action). It examined published material for serious adverse events, used FDA information, and discussed serious adverse events with trialists and manufacturers for clarification. The denominator was the number of patients with at least one dose of drug, and the numerator patients with at least one serious malignancy or infection. Nine trials lasting at least 12 weeks (eight were six months to one year) randomised 5,014 patients.

A separate analysis of etanercept [2] included 4,322 patients in 22 trials, with almost 7,000 patient years of follow up, using an integrated safety database.

Malignancy

There were 29 malignancies in 3,192 patients (0.9%) on infliximab or adalimumab, and 3 in 1,428 (0.2%) on placebo (Figure 1); six other lymphomas were detected during follow up, but not included in the analysis. The odds ratio was 3.3 (1.2 to 9.1), and the number of patients who needed to be treated for six to 12 months with infliximab or adalimumab for one to be harmed was 154 (91 to 500).

With etanercept the number of malignancies was not given, but it was claimed that the incidence of overall malignancies remained stable with time and was comparable to that expected in the rheumatoid arthritis population.

Figure 1: Cancer rates in randomised trials of infliximab and adalimumab in RA

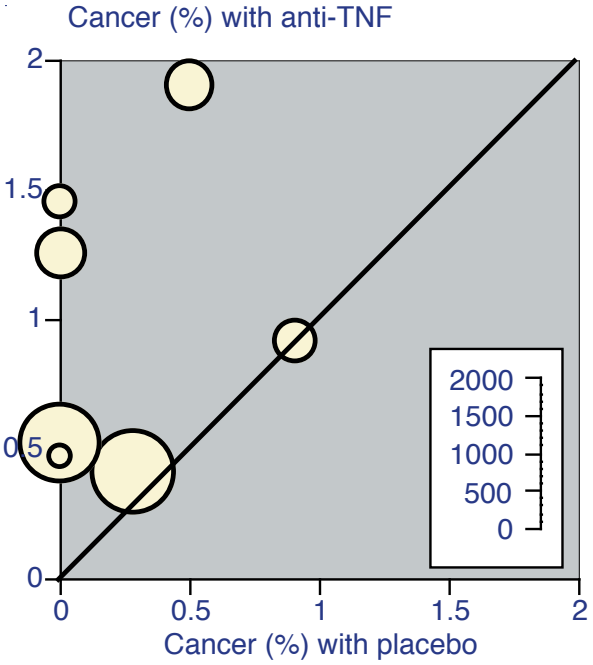
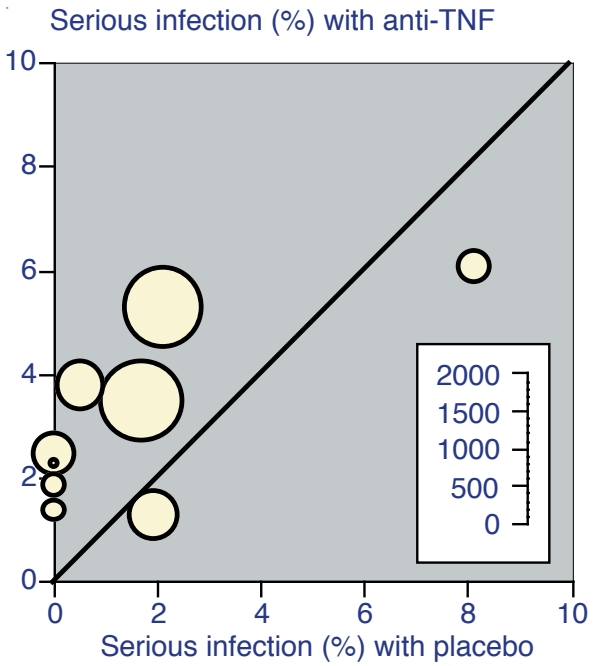


Figure 2: Serious infection rates in randomised trials of infliximab and adalimumab in RA



Serious infections

There were 126 serious infections in 3,493 patients (3.6%) on infliximab or adalimumab, and 26 in 1,512 (1.7%) on placebo (Figure 2). The odds ratio was 2.0 (1.3 to 3.1), and the number of patients who needed to be treated for six to 12 months with infliximab or adalimumab for one to be harmed was 59 (39 to 125).

For etanercept, medically important infections (intravenous antibiotic or hospital admission) were claimed not to be higher than in control groups.

Observational studies

A series of observational studies come from Sweden [3-5], where the mix of anti-TNF treatments was predominantly etanercept and infliximab. These used several sources of information, a prevalent cohort of 53,000 rheumatoid arthritis patients, an incidence cohort of 3,700 rheumatoid arthritis patients, and one rheumatoid arthritis cohort of 4,160 patients treated with TNF antagonists. These had approximately 300,000, 13,000, and 10,000 person years of follow up respectively, with average follow ups of 6, 3.5 and 2.5 years per patient.

Linkage between different registries and cancer and other registries meant that outcomes could be collected. The entire Swedish population served as a control group for calculation of standardised rates.

Malignancies

Haematopoietic malignancies [3] occurred in 507 patients, at rates higher than the general population (Table 1). When compared with the prevalent and incident rheumatoid arthritis cohorts not receiving TNF, patients receiving TNF antagonists had a relative risk of 1.1 (95% CI 0.6 to 2.1).

Solid cancers [4] occurred in 3,584 patients, at rates little greater than in the general population (Table 1). When compared with the prevalent and incident rheumatoid arthritis cohorts not receiving TNF, patients receiving TNF antagonists were little different (Table 1) overall, or when analysed by duration of observation.

Serious infections

The evidence here comes from another analysis of cohort studies in Sweden [5]. It was limited by the small number of tuberculosis cases in patients treated with infliximab or etanercept (15, 10 of them pulmonary). Only four of these were included in a statistical analysis. The best guess is that tuberculosis rates are increased in rheumatoid arthritis patients treated with TNF antagonists.

Table 1: Cancer rates in observational study of infliximab and etanercept in Sweden

RA cohort	Haematopoietic malignancies	Patient years of observation	Standardised incidence rate (95% CI)
Haematopoietic malignancy			
Prevalent	481	297102	1.7 (1.5 to 1.8)
Incident	15	13292	1.6 (0.9 to 2.6)
Anti-TNF	11	9715	2.1 (1.1 to 3.8)
Solid cancer			
Prevalent	3379	297102	1.05 (1.01 to 1.08)
Incident	138	13292	1.1 (0.9 to 1.3)
Anti-TNF	67	9715	0.9 (0.7 to 1.2)

Comment

It is always tempting to dismiss observational studies when they disagree with randomised trials (or meta-analyses of them). This may be hasty, especially when both types of study are well done. It is always worth asking a few questions, especially when we are dealing with serious, but rare, adverse events.

The first question is about size, about the number of events. Because they are rare events, malignancies and serious infections are unlikely to be numerous. If a statistical analysis is based on a handful of events, potential interference from the random play of chance is possible. One meta-analysis, for instance, had three malignancies with placebo, and one observational study used four and two cases of tuberculosis to calculate statistics.

While on size, observational studies can involve a lot of patients, and here observational studies had up to four times as many patient years of observation than did a meta-analysis of randomised trials.

Which brings us to time, especially important for adverse events. Some may occur early with treatment, others late, or they can be constant over time. Comparing short with long duration studies can be problematical.

And finally, what treatments are being used? None of the observational studies seemed to include adalimumab, or any other newer agents. So while meta-analyses concentrated on some agents but not others, observational studies reported on a different mix of agents being used in clinical practice. The question, then, is whether we are comparing like with like.

If there is an lesson here, it is that for serious but rare adverse events, rushing to judgement may not be prudent. If there is an answer, it is that tinkering with the immune system can produce great benefit, but with a risk of something bad happening. Until we can say with certain who will benefit and who will be at risk, we have to live with that uncertainty.

Reference:

1 T Bongartz et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies. JAMA 2006 295: 2275-2285.
2 R Fleischmann et al. Long term safety of etanercept in elderly subjects with rheumatic diseases. Annals of the Rheumatic Diseases 2006 65: 379-384.
3 J Askling et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Annals of the Rheumatic Diseases 2005 64: 1414-1420.
4 J Askling et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Annals of the Rheumatic Diseases 2005 64: 1421-1426.
5 J Askling et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumour necrosis factor antagonists in Sweden. Arthritis & Rheumatism 2005 52: 1986-1992.

BISPHOSPHONATES AND JAW OSTEONECROSIS

Rare adverse events are now often reported in the media as well as in medical journals. It makes for a good story, after all, because it is easier to scare than to reassure. It seems humans are hard wired to believe the worst.

So it has been for bisphosphonates and osteonecrosis of the jaw. A quick look for news items confirms headlines like "*Are drugs for bones a threat to jaws?*", followed by the information that lawyers are looking for patients who want to sue a drug company. Adverse events get particularly to the financial pages.

For the many older women and men who take bisphosphonates to strengthen bones, this is a potential worry. It is also difficult for professionals to get a handle on, especially when it comes to reassuring or informing patients. A systematic review often helps.

Systematic review [1]

The systematic review used searches to the end of January 2006, making it current. It used two electronic databases for studies linking jaw osteonecrosis with bisphosphonates. It reviewed all the case reports and case series, and included those with acceptable documentation of disease and use of bisphosphonates. They were particular about including only one report per patient, as this is an area replete with multiple publications.

Results

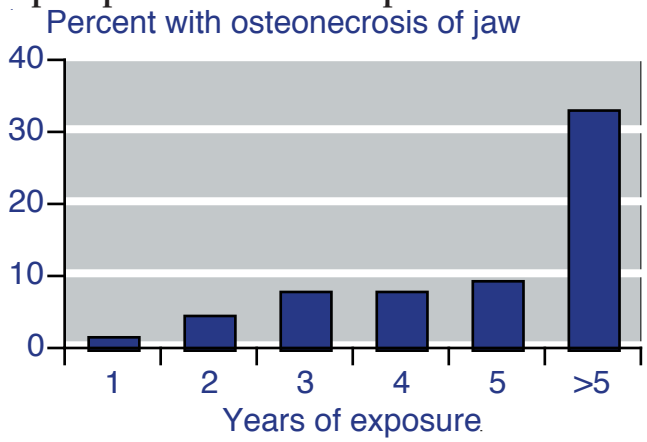
There were 368 cases of bisphosphonate-associated osteonecrosis of the jaw (Table 1). Almost all of them (95%) occurred in people being treated for cancer (where larger intravenous doses of bisphosphonates are used), and only 15 cases occurred in people treated for osteoporosis (involving lower, oral, doses). Intravenous palmidronate or zoledronic acid were most often used in cancer patients.

Tooth extraction or oral surgery was a factor in 60% of the cases, and the 40% that did not often involved people using dentures, or who had some other oral health problem.

Table 1: Cases of osteonecrosis of the jaw associated with bisphosphonates from a systematic literature review

Diagnosis	Number of cases	Percent of total
Multiple myeloma	171	47
Metastatic breast cancer	143	39
Metastatic prostate cancer	23	6
Other metastatic disease	13	3
All malignancy	350	95
Osteoporosis	15	4
Paget disease of bone	3	1

Figure 1: Incidence of osteonecrosis of the jaw with duration of exposure to intravenous bisphosphonates in cancer patients



The most important risk factors for developing bisphosphonate-associated osteonecrosis of the jaw were type and total dose of bisphosphonate and history of trauma, dental surgery, or dental infection.

A closer look at incidence studies in cancer patients can be helpful to give more background. For instance, a retrospective examination [2] of 252 cancer patients receiving at least six bisphosphonate infusions and followed up for at least two years recorded 17 cases (7%) of osteonecrosis of the jaw. There was a higher incidence in multiple myeloma (10%), with lower rates for breast and other cancers. Patients developing osteonecrosis had received more bisphosphonate infusions (35 vs 15 in those not developing osteonecrosis) and had longer exposure (39 months vs 19 months). There is a suggestion that incidence of jaw osteonecrosis could be very significant in long term users with many infusions (Figure 1), though with small numbers.

Incidence of jaw surgery

Another way of looking at the effects of bisphosphonates might be to use a surrogate to diagnosis of osteonecrosis, like jaw surgery. A database analysis of 256,000 patients with breast, lung, or prostate cancer was analysed for jaw surgery [3].

There were 224 cases of jaw surgery. Of these 185 cases occurred in 229,000 who never used bisphosphonates, while 39 occurred in 26,000 patients given bisphosphonates. Table 2 shows the event rates for jaw surgery according to bisphosphonate use. Oral use was not significantly different from non-use, but with intravenous use jaw surgery was about four times more frequent.

Table 2: Cases of jaw surgery associated with bisphosphonates in an observational study in cancer patients

Bisphosphonate use	Number with jaw surgery	Total number	Rate (1 in)
None	185	229,470	1240
Intravenous	20	5,850	293
Oral	19	20,438	1076

Comment

The bulk of the reported cases are in patients being treated for cancer, where bisphosphonates reduce bone pain, and significantly reduce bone problems. There are clear risk factors, and newer guidance places great emphasis on oral examinations before starting treatment with bisphosphonates in cancer patients, and maintaining good oral health.

Cancer patients receive high doses of bisphosphonates intravenously. Osteoporosis patients receive much lower doses orally. Here the risk is much lower, with only 15 reported cases.

The problem, of course, is that not all cases get reported in the literature. A quick scan of the Internet suggests that many more have been reported using established yellow card systems. Most of these appear, again, to be cancer patients. Few reports relate to oral bisphosphonates, with perhaps 150 cases in the USA, and fewer than 10 in the UK. Given the millions of people taking oral bisphosphonates, the risk is negligible. Maintaining good oral health in older people still makes sense, as does exchange of information on drugs by dentists and patients.

References:

1 SB Woo et al. Systematic review: bisphosphonates and osteonecrosis of the jaws. Annals of Internal Medicine 2006 144: 753-761.

2 A Bamias et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. Journal of Clinical Oncology 2005 23: 8580-8587.

3 AI Zavras, S Zhu. Bisphosphonates are associated with increased risk for jaw surgery in medical claims data: is it osteonecrosis? Journal of Oral and Maxillofacial Surgery 2006 64: 917-923.

MI RATES FALLING

We expend considerable effort in trying to reduce heart attacks. Interventions include exhortation to better lifestyle (smoking cessation, exercise, weight control, and healthy diet) and drugs (including cholesterol reduction and blood pressure control). Feedback is important, particularly knowing that the totality of our efforts is having some beneficial result. An examination of hospital admission rates for myocardial infarction from the whole of Holland [1] is encouraging.

Study

Patients admitted to hospital for first myocardial infarction in 1995 and in 2000 were identified through a national hospital discharge register, and this was linked to a national population register. Admissions were used if they were unique, were first admissions, and were residents in Holland. Incidence rates were calculated using the number of people in the population as the denominator.

Figure 1: Incidence of hospital admission for first myocardial infarction in women

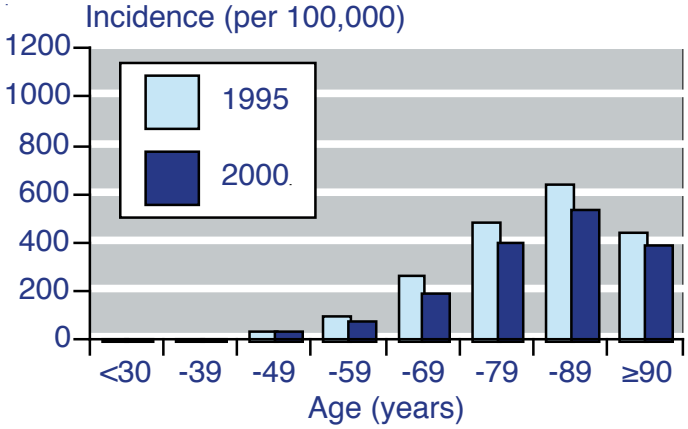
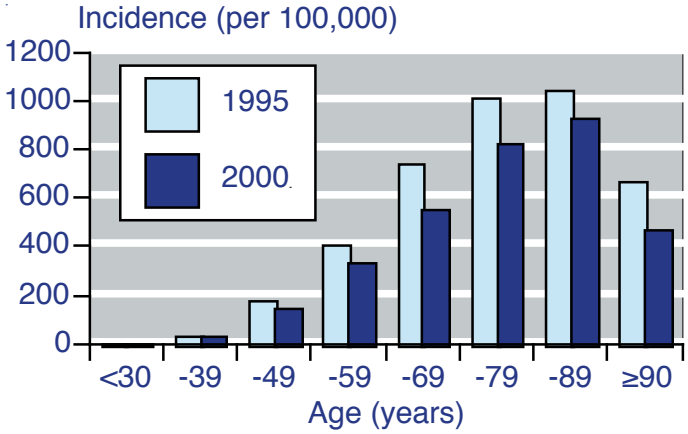


Figure 2: Incidence of hospital admission for first myocardial infarction in men



Results

The final cohorts included 21,500 admissions for myocardial infarction in 1995, and 19,000 in 2000. The mean age for women was 72 years and for men 67 years. Figures 1 and 2 show the incidence rates by age for women and men respectively. At almost all ages the incidence was lower in 2000 than it was in 1995. In women the overall incidence fell from 106 to 91 per 100,000, a 14% fall. In men the overall incidence fell from 221 to 190 per 100,000, again a 14% fall. The age-standardised incidence fell by 17% for women and 19% for men.

Comment

Studies have been showing reductions in myocardial infarction rates in western countries for some years, from the mid-1970s in the USA (Bandolier 119), though it is unusual to see the decrease computed for a whole county. Since 2000, interventions to reduce heart disease have increased, with a much greater awareness of the major impact of healthy lifestyles, reducing smoking rates generally, and much more use of drug intervention, for instance to reduce levels of cholesterol. It is interesting to speculate how much more is likely to be achieved when more recent studies report.

Reference:

1 HL Koek et al. Decline in incidence of hospitalisation for acute myocardial infarction in the Netherlands from 1995 to 2000. Heart 2006 92: 162-165.

Communicating evidence

One of the real frustrations about evidence is the disconnect between what the evidence is, and what the perceptions may be, with the clearest example being MMR. Each day millions of important decisions are being taken by professionals and their patients, part of which involves communicating evidence of benefit and risk, so that informed choices can be made. Do we know the best way of doing this?

Systematic review

The simple answer is that we do not, but a systematic review [1] begins helping us think about it. The review sought studies relating to three questions about strategies of effective communication. These related to the most effective decision tools, the most effective formats to represent probabilistic information, and the most effective way to elicit patient preferences.

Results

Predictably there is no simple answer to an incredibly complex question, in part because there is so little research. A few points emerge worth noting:

1 Information should be structured or interactive.
2 Ideally it should be tailored to the individual as much as possible.
3 Natural frequency formats should be used to convey numbers.
4 Pictures and graphs can help convey numeric information.
5 Written information is helped by pictures or graphs.

Comment

No surprises here, then, especially for Bandolier readers following our attempts to find some clarity. It helps to see that others find nothing much more, and it helps to define research agendas. There are opportunities here for simple, inexpensive, but important research.

The review is perhaps most important because it demonstrates an enormous black hole in the whole business of evidence. If finding trustworthy evidence is hard enough, knowing how best to tell people about it is a black hole. We struggle communicating with healthcare professionals, with industry, and with government. In the absence of evidence about communicating effectively with patients, because we know so little, we should assume we do it badly.

Communicating evidence is important in a patient-led service, but there are pitfalls. The biggest is when the evidence is that what patients want and what we do are diametrically opposed.

Reference:

1 LJ Trevena et al. A systematic review on communicating with patients about evidence. Journal of Evaluation in Clinical Practice 2006 12: 13-23.

Occult blood tests for colorectal cancer?

People get hot under the collar when it comes to screening, and screening for cancer in particular. Two general criticisms are often made of screening trials. First that the design of many studies was compromised, resulting in possible bias, with better studies giving less encouraging results (as for breast cancer screening in Bandolier 72). The other is that results of screening are provided in terms of death reduction for the cancer being screened, not all cause mortality.

For instance, a Cochrane review [1] of occult blood testing for colorectal cancer screening found that biannual occult blood screening reduced colorectal cancer deaths by about 20%, preventing about one death per year per 10,000 people. Comments on that review include the criticism of the failure to analyse overall deaths, but that has now been done [2], and provides interesting reading.

Meta-analysis

The original Cochrane review included four randomised trials, but did not report overall deaths. Two have now published more follow up, allowing the analysis to be done.

Results

Three of the four trials in the original review provided data, on 245,000 people, with 2.8 million years of follow up, and using biannual screening. There were 2,148 colorectal cancer deaths, and 65,000 deaths in total.

The death rate from colorectal cancer was about 1 in 100 people over the whole period, or 1 in 1,250 per year. As in the Cochrane review, colorectal cancer deaths were reduced with screening, though the absolute effect was small, almost 10,000 people needing to be screened for one year to prevent a single colorectal cancer death. Table 1 shows the analysis as per patient, and per patient year.

The death rate from all causes was 1 in 4 over the whole period, about 1 in 40 per year. Neither analysis by patient nor by per patient year showed any difference between the screened and the control population in terms of overall mortality.

Comment

The corollary of all this was that screened persons died more often from other causes, significantly so. How could such a result be possible? It is unlikely that biannual occult blood testing would, in itself, be a cause of death.

The most obvious point is that only 1 death in 30 was a colorectal cancer death. Moreover, the difference between screened and non-screened people was only 1 death in every 300 total deaths. How likely is it, then, that a difference this small would be seen in an analysis of overall mortality. The answer is that it is vanishingly small, even with large numbers of patients observed over many years; it would be washed out by the random play of chance.

It may also just be possible that the fact of screening could give a false sense of health security, with a greater tendency to less healthy lifestyle. Another possibility would be that these open trials could be open to bias, with more intensive investigation for people being screened.

The final word, though, should be on the balance between benefit and risk. We know that over 80% of positive tests were false; the tests were positive but patients did not have cancer [1]. Those patients had the stress of receiving a positive test, and underwent further examination, which is not entirely benign. In 10,000 people an estimated 60-280 would have at least one colonoscopy, with 2-4 perforations or haemorrhages.

Some of these will be fatal. So for occult blood screening for one year, the chance of avoiding dying from colon cancer is 1 in 1,200, while the risk of a perforation or haemorrhage is 1 in 3,000. Maybe it is better and more productive to get people to eat more fibre, especially when we can be pretty sure that screening in practice is unlikely to be as thorough as screening in trials.

Reference:
1 BP Towler et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database of Systematic Reviews issue 2, 1998.
2 P Moayyedi, E Achkar. Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. American Journal of Gastroenterology 2006 101: 380-384.

Table 1: Meta-analysis of colorectal cancer deaths and death from all causes, with biannual occult blood screening

Analysis	Number of patients/ patient years	Percent deaths		Relative Risk (95% CI)	NNT to prevent one death from colorectal cancer
		Screening	Control		
Colorectal cancer deaths (n=2,148)					
Per patient	245,217	0.82	0.94	0.87 (0.80 to 0.95)	830 (520 to 2,200)
Per patient per year	2,757,795	0.083	0.073	0.87 (0.80 to 0.95)	9,400 (5,800 to 25,000)
Deaths from all causes (n=64,949)					
Per patient	245,217	26.5	26.5	1.00 (0.99 to 1.01)	not calculated
Per patient per year	2,757,795	2.36	2.35	1.00 (0.98 to 1.02)	not calculated

Bandolier has only dipped a toe into these waters, agitated as they are by disagreement over whether the condition exists, diagnosis, and whether any treatments, of whatever sort, work. Readers press for a less insipid approach, so a quick traipse through some recent(ish) reviews and trials.

A word of caution, though, is needed. Fibromyalgia trials come with different inclusion criteria, suggestions of differences between women and men, and different outcomes (pain, sleep, trigger point numbers or tenderness, as a few examples). There is no comprehensive whizzo treatment that does what it says on the tin, so we are always looking for small gains, not cures.

Antidepressants

A systematic review published in 2000 [1] included nine randomised trials, only some of which were double blind. It included three cyclobenzaprine studies, even though cyclobenzaprine is classified as a muscle relaxant. The remaining studies were small, and we are given only effect sizes, which showed a moderate effect for a variety of outcomes, including global assessment and pain.

Newer antidepressant studies

Since this review we have at least three more small studies involving amitriptyline, and three more large randomised trials, two on duloxetine and one on milnacipran.

As duloxetine is available it is worth looking at the studies [2,3]. Both enrolled patients with fibromyalgia using ACR (American College of Rheumatology) criteria, and with at least moderate pain, and had sensible exclusions. One was exclusively, and one predominantly in women. In the 532 randomised women, 38% had at least 50% improvement in pain over 12 weeks with 60 mg duloxetine (once or twice a day), compared with 21% with placebo. The NNT was 5.8 (4.0 to 10). There were improvements in quality of life, and more adverse events with duloxetine, especially nausea and dry mouth.

Cyclobenzaprine

Five randomised trials were included in a meta-analysis [4], but neither trials nor review appear to be of a particularly high standard. The best that can be said is that there may be an NNT of about 5 for symptom improvement.

Pregabalin

We found only a single study [5] looking at an anticonvulsant. Here, pregabalin at three dose levels was compared with placebo over eight weeks in 529 patients (90% women) with ACR-defined fibromyalgia, with at least moderate initial pain.

There was a strong dose-response, with only the top dose of 450 mg/day pregabalin being significantly different from placebo. At least 50% reduction in pain was achieved by 29% of patients on pregabalin 450 mg, compared with 13% on placebo. The NNT over eight weeks was 6.3 (3.9 to 16). Adverse events included dizziness, somnolence, and dry mouth.

Comment

The results are summarised in Table 1. On the whole, not a body of evidence to be comfortable about. There is a crying need for a robust, evidence-based approach, applying criteria of quality, validity, and size, to help get a grip.

It is also important to acknowledge that fibromyalgia attracts many other interventions, including exercise, lifestyle modification, and some rather more peculiar ones. It is clear that there is no quick fix, which makes a sensible approach even more imperative to avoid chasing after ephemera.

References:

1 LM Arnold et al. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000 41: 104-113.
2 LM Arnold et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis & Rheumatism 2004 50: 2974-2984.
3 LM Arnold et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005 119: 5-15.
4 JK Tofferi et al. Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. Arthritis & Rheumatism 2004 51: 9-13.
5 LJ Crofford et al. Pregabalin for the treatment of fibromyalgia syndrome. Arthritis & Rheumatism 2005 52: 1264-1273.

Table 1: Summary of evidence for drug interventions in fibromyalgia

Intervention	How good is the evidence	Efficacy
Older antidepressants	A mixed bag of a small number of small trials, never really evaluated for quality or validity.	Indication of moderate effect size, but with probability of some bias
Duloxetine	Two good, modern, randomised double blind trials, using ACR criteria, largely on women	NNT about 6 for ≥50% pain reduction
Cyclobenzaprine	No confidence that this evidence can be trusted because of possible deficiencies in trials and review	NNT of about 5 for some symptom improvement, but residual bias likely
Pregabalin	One trial, with only one arm effective, so efficacy data limited to about 260 patients. Good randomised, double blind trial using ACR criteria, largely on women	NNT about 6 for ≥50% pain reduction

BNP FOR AF - UPDATE

Systematic review and meta-analysis of good studies of diagnostic tests are rare. One on BNP tests for congestive heart failure is important as diagnosis is not easy in primary care because symptoms are unspecific. Diagnosis usually requires expensive echocardiography or radionuclide scan. BNP ruling out heart failure would save money and time.

Systematic review

The review [1] had a thorough search of general and specialist diagnostic test databases. Studies compared any type of BNP assay in asymptomatic patients or those with suspected congestive heart failure with gold standard of echocardiography or radionuclide scan, with or without additional diagnostic criteria, and have information on true and false positive and negative. Cut off was that used by studies.

Results

Nineteen studies on 22 populations with 9,093 patients were available. Studies were generally of good quality, with prospective design, consecutive cohort, and blind test interpretation of test results common. Mean ages ranged from 51 to 79 years, and percentage of men from 35% to 95%. Some studies examined secondary care patients (acute dyspnoea, after myocardial infarction, with an existing diagnosis of heart failure), others primary care referrals, and some were screening studies of patients with risk factors.

The results for ELISA and RIA methods are shown in Table 1 as the proportion of all positive tests that were true positives and the proportion of all negative tests that were true negatives. The ideal test would score 100% for both. The proportion of patients who actually had heart failure by gold standard method varied from 50-60% in the secondary care setting, to about 20% in patients referred from general practice, and was 5% in screening studies. Where prevalence was low, both types of tests reliably ruled out heart failure, so that a negative test meant patients did not have heart failure.

Comment

These tests are not cheap, but the gold standard diagnostic test is much more expensive. In a primary care population of 1,000 people in whom the GP has a clinical suspicion of heart failure, 200 will actually have heart failure and 800 will not. Figure 1 shows how the test will work out if we assume that in this population it picks up 50% of true positives and excludes 96% of true negatives.

Of the 1,000 patients, the test would mean that 868 would not be sent for confirmatory testing, while 132 would be sent for confirmatory testing. The ratio of about 7 patients not sent for confirmatory testing because of the result of the BNP testing for every one sent for confirmation would imply cost saving if the confirmatory test cost about £100 or more, though it would also have major implications for waiting times.

The concern might be that 100 patients who truly had heart failure would not have confirmatory testing. Presumably these would be less severe cases that might return later to the GP, and would have other tests. More detailed thinking is needed to fully appreciate the possible cost-effectiveness on BNP testing in primary care.

Reference:
1 M Battaglia et al. Accuracy of B-type natriuretic peptide tests to exclude congestive heart failure. Archives of Internal Medicine 2006 166: 1073-1080.

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Figure 1: Results in a hypothetical primary care population of 1,000 people where GP suspects heart failure

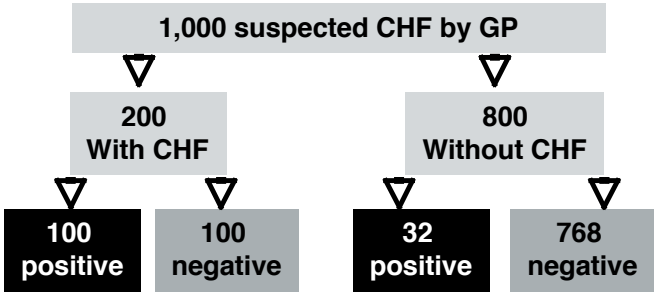

Table 1: Results of BNP tests by ELISA or RIA in different populations with varying proportions of patients with true heart failure defined by gold standard diagnostic methods

	ELISA				RIA			
Population	Number of subjects	True HF (%)	True positive/ all positive (%)	True negative/ all negative (%)	Number of subjects	True HF (%)	True positive/ all positive (%)	True negative/ all negative (%)
All studies	2963	40	72	92	6130	11	28	98
Secondary care	1839	50	81	89	310	60	82	71
Primary care	1124	22	51	97	1391	17	32	96
Screening					4429	5	17	99